REVIEW ARTICLE

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Management of Cerebral Edema, Brain Compression, and Intracranial Pressure

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ABSTRACT

PURPOSE OF REVIEW: **This article reviews the pathophysiology and management of cerebral edema, brain compression, and elevated intracranial pressure (ICP). It also provides a brief introduction to the concept of the glymphatic system and select cellular contributors to cerebral edema.**

RECENT FINDINGS: **Cerebral edema and brain compression should be treated in a tiered approach after the patient demonstrates a symptomatic indication to start treatment. All patients with acute brain injury should be treated with standard measures to optimize intracranial compliance and minimize risk of ICP elevation. When ICP monitors are used, therapies should target maintaining ICP at 22 mm Hg or less. Evidence exists that serial clinical examination and neuroimaging may be a reasonable alternative to ICP monitoring; however, clinical trials in progress may demonstrate advantages to advanced monitoring techniques. Early decompressive craniectomy and hypothermia are not neuroprotective in traumatic brain injury and should be reserved for situations refractory to initial medical interventions. Medical therapies that acutely lower plasma osmolality may lead to neurologic deterioration from osmotic cerebral edema, and patients with acute brain injury and renal or liver failure are at elevated risk.**

SUMMARY: **A tiered approach to the management of cerebral edema and brain compression can reduce secondary brain injury when implemented according to core physiologic principles. However, our knowledge of the pathophysiology of acute brain injury is incomplete, and the conceptual framework underlying decades of clinical management may need to be revised in response to currently evolving discoveries regarding the pathophysiology of acute brain injury.**

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INTRODUCTION

The management of cerebral edema, elevated intracranial pressure (ICP), and brain compression from space-occupying lesions is central to the care of patients with acute brain injury. Although these entities often coexist, they are distinct, and differences in injury mechanism and clinical presentation refine the management. Historically, management strategies have been rooted in a few core physiologic principles, as

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discussed later in the article: the Monro-Kellie doctrine and intracranial compliance, the relationship between ICP and cerebral perfusion pressure (CPP), cerebral autoregulation and the coupling of cerebral blood volume to cerebral metabolism, and the movement of water between tissues driven by osmotic gradients. Moreover, a rather limited number of therapeutic interventions have been based on these physiologic principles; hyperosmolar therapy and supportive medical care—along with selective use of analgesics, anesthetics, CSF diversion, and occasional surgical decompression or induced hypothermia—remain the core interventions for cerebral edema, elevated ICP, and brain compression. These core interventions are rather blunt instruments in that they do not distinguish between or specifically target the multitude of cellular mechanisms underlying cerebral edema formation, and they are principally used after cerebral edema or elevated ICP has already developed. However, the management of cerebral edema may be at a turning point. Recent discoveries concerning the anatomy of the brain and the cellular mechanisms dictating cerebral fluid movement may result in future therapies that target specific cerebral edema mechanisms. This article reviews the current concepts important for the clinical understanding and management of cerebral edema, elevated ICP, and brain compression. The article concludes by introducing the recently discovered glymphatic system and select cellular mechanisms that may come to change the conceptual framework and interventions by which cerebral edema and ICP are clinically managed.

CEREBRAL EDEMA

The term *cerebral edema* essentially denotes an increase in brain water content that leads to brain volume expansion. Cerebral edema may occur either focally or diffusely and may be encountered after any type of primary injury to the brain as well as in some systemic medical conditions, such as acute or acute-on-chronic liver failure.[1,2] Identifying cerebral edema is clinically important because it is a major cause of secondary brain injury (following a variety of primary insults) through compression of brain structures, distortion and herniation of brain tissue, and compromise of cerebral blood flow through increased ICP.[3] Clinically, cerebral edema is indirectly measured by its appearance on imaging studies (such as low attenuation on CT, increased T2 signal on MRI, or tissue shifts) or, when cerebral edema is sufficiently advanced, by the development of increased ICP when invasive monitoring is available. The qualitative identification of cerebral edema and delineation of its pattern on imaging studies may also be useful when a differential diagnosis for acute neurologic dysfunction is not immediately apparent from history and physical examination (**CASE 1-1**). Furthermore, identifying the dominant type of cerebral edema based on neuroimaging pattern and injury mechanism can guide initial treatment strategies to minimize secondary brain injury. Clinicians should be aware of four forms of cerebral edema: vasogenic, cytotoxic, hydrostatic, and osmotic. Vasogenic and cytotoxic edema are the most frequently encountered, and their mechanisms have received the most attention.[2]

Vasogenic edema (**FIGURE 1-2**) results from dysfunction of the blood-brain barrier, the physical and metabolic barrier between the brain and the systemic circulation that is formed by endothelial cells, the tight junctions between endothelial cells, astrocytes, and pericytes. Blood-brain barrier dysfunction results in extravasation of ions and macromolecules from the plasma; these ions

KEY POINTS

- Cerebral edema is a major cause of secondary brain injury through compression of brain structures, distortion and herniation of brain tissue, and compromise of cerebral blood flow through increased intracranial pressure.
- Clinicians should be aware of four forms of cerebral edema: vasogenic, cytotoxic, hydrostatic, and osmotic. Vasogenic and cytotoxic edema are the most frequently encountered.
- Vasogenic edema results from dysfunction of the blood-brain barrier, the physical and metabolic barrier between the brain and the systemic circulation. It is associated with brain tumors, cerebral abscesses, and posterior reversible encephalopathy syndrome.

CASE 1-1

A 58-year-old woman presented to the emergency department comatose after being found unresponsive by her neighbors, who were unable to provide additional history. Her initial systolic blood pressures were 140 mm Hg to 150 mm Hg. A head CT demonstrated hypoattenuation of the bilateral posterior white matter in a pattern consistent with severe posterior reversible encephalopathy syndrome (PRES) (FIGURE 1-1A).[4] Subsequent T2-weighted/fluid-attenuated inversion recovery (FLAIR) MRI demonstrated hyperintense signal consistent with vasogenic edema in the posterior white matter and involvement of the brainstem (FIGURE 1-1B). Diffusion-weighted imaging (DWI) MRI also revealed hyperintensity (FIGURE 1-1C) with corresponding hypointensity on apparent diffusion coefficient MRI (FIGURE 1-1D), suggesting cytotoxic edema involving the left parietal, occipital, and medial temporal cortex. Three hours after presentation, the patient developed sustained systolic hypertension to 220 mm Hg and required nicardipine infusion for blood pressure control. EEG confirmed nonconvulsive status epilepticus with seizures arising from the left medial temporal lobe. She improved neurologically after treatment of status epilepticus and intermittent severe hypertension.

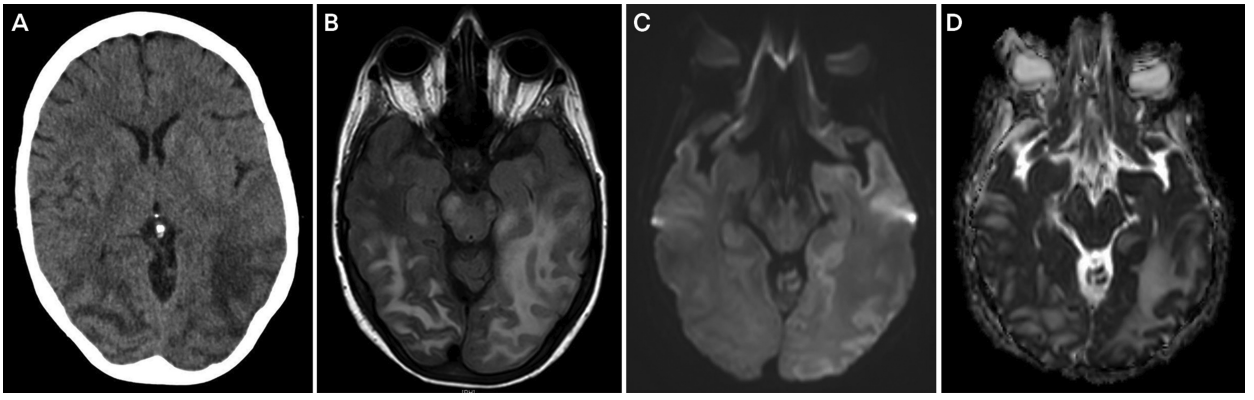

FIGURE 1-1
Imaging of the patient in CASE 1-1. *A*, Axial head CT shows hypoattenuation of the bilateral posterior white matter in a pattern consistent with posterior reversible encephalopathy syndrome (PRES). *B*, Axial fluid attenuated inversion recovery (FLAIR) MRI shows hyperintense signal consistent with vasogenic edema in the posterior white matter and involvement of the brainstem. *C*, Axial diffusion-weighted MRI shows hyperintensity, suggesting cytotoxic edema involving the left parietal, occipital, and medial temporal cortex that is confirmed by axial apparent diffusion coefficient MRI hypointensity (*D*).

COMMENT

This case demonstrates that cerebral edema patterns can be useful in directing the initial management of patients with undifferentiated coma. Bilateral posterior-predominant vasogenic edema raised suspicion for PRES, even in the initial absence of significant hypertension. Although empiric seizure management and EEG were initiated in response to the patient's CT scan, the presence of cortical DWI hyperintensity could have alerted the clinician to the possibility of cytotoxic edema from status epilepticus.

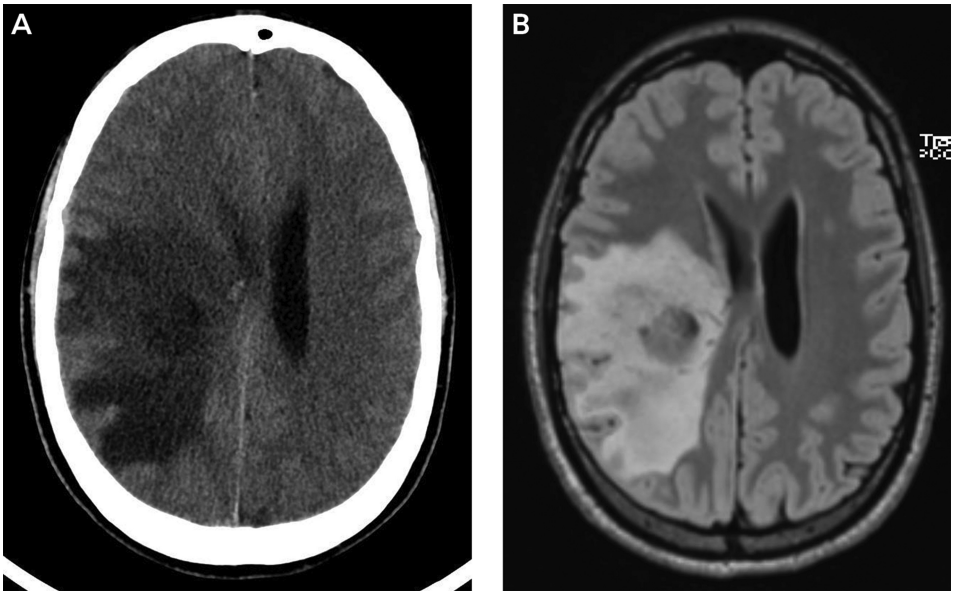

FIGURE 1-2

A 30-year-old man presented with severe headaches and left-sided face, arm, and leg numbness and was found to have a right hemispheric grade 3 anaplastic astrocytoma. Axial noncontrast head CT (*A*) and fluid-attenuated inversion recovery (FLAIR) MRI (*B*) show the typical pattern of vasogenic edema expected with a brain tumor. Signal abnormality extends along the white matter and appears to respect the boundary with the gray matter, creating a fingerlike appearance. The tumor can be appreciated encased by surrounding edema. An element of brain compression in the form of right lateral ventricle compression is seen.

and macromolecules generate an osmotic pressure, which, combined with vascular hydrostatic pressure, results in net movement of water into the brain.[2] The resulting water expands the extracellular space and collects preferentially in the subcortical white matter, giving an appearance of hypoattenuated white matter on CT and hyperintense white matter on T2-weighted MRI without diffusion restriction and sparing of the cortical and deep gray matter. Vasogenic edema is classically associated with brain tumors, cerebral abscesses, and posterior reversible encephalopathy syndrome (PRES). An important advance in the understanding of vasogenic edema was the observation that frank blood-brain barrier disruption visible on microscopy is not necessary. Abnormal transcellular transport across endothelial cells and degradation of endothelial tight junctions by proteolytic enzymes, such as matrix metalloproteinase-9, can contribute to vasogenic edema by the passage of ions, proteins, and water from the plasma despite a blood-brain barrier that appears intact on microscopy.[1,2]

Cytotoxic edema (FIGURE 1-3) results from derangements in cellular metabolism with resulting alterations in ionic gradients and movement of water into the brain tissue. It is important to note that this article and most clinicians use the term *cytotoxic edema* to refer to brain swelling that results from failure of cellular metabolism; basic scientists use the term differently. When brain cells die, they lose the ability to maintain normal ionic gradients; as a result, ions and water move from the extracellular space to the intracellular space and the brain cells expand. This process, called *true cytotoxic cellular edema* by basic scientists, is a redistribution of fluid without a net increase in tissue volume. As a result of this process, the extracellular space develops an ion deficiency. If the extracellular

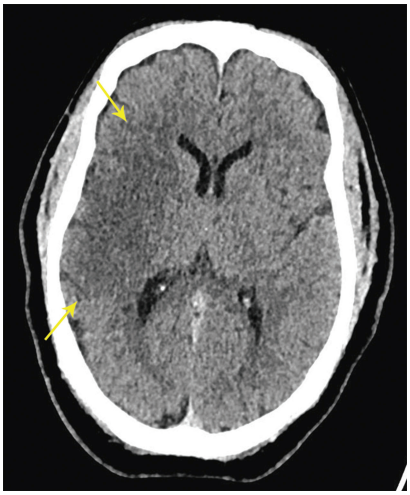

FIGURE 1-3
A 66-year-old man was admitted to the medical floor for pulmonary symptoms related to COVID-19. During the hospitalization, he developed new-onset atrial fibrillation. The next day, he experienced acute-onset left hemiparesis and was found to have acute occlusion of the right middle cerebral artery. Axial noncontrast head CT obtained 5 hours after neurologic symptom onset shows subtle hypoattenuation involving the white and gray matter of the right middle cerebral artery territory consistent with early cytotoxic edema.

space is then exposed to a fluid source, such as vascular blood flow or CSF,[2,5] ions and water can flow down an ionic gradient from the fluid source to the extracellular space; this results in expansion of the extracellular space that, combined with the previous fluid redistribution, causes a net increase in brain tissue volume through the process of ionic edema. The clinical term *cytotoxic edema* refers to the combined process of true cytotoxic cellular edema and ionic edema resulting in tissue swelling. These semantics are useful to remind clinicians that ultimately all brain swelling requires the brain to be perfused with an external source of new fluid. Since cytotoxic edema affects both white and gray matter, cytotoxic edema appears as CT hypoattenuation of both white and gray matter; on MRI, T2 hyperintensity affecting both white and gray matter is seen, accompanied by hyperintensity on diffusion-weighted imaging (DWI), representing true cytotoxic cellular edema. Cytotoxic edema is classically associated with ischemic stroke and acute liver failure. Additionally, cytotoxic edema predominates in hypoxic-ischemic brain injury, and traumatic brain injury (TBI) and intracerebral hemorrhage include components of both cytotoxic and vasogenic cerebral edema. Although cellular death often occurs, cellular metabolic stress that impairs normal ionic homeostasis—as can be seen with prolonged seizures (**CASE 1-1**), liver failure, or various toxic exposures—is sufficient to result in cytotoxic edema.

Although it may be clinically useful to identify whether cytotoxic or vasogenic edema predominates and attribute each to particular diseases, these distinctions are somewhat artificial. Vasogenic edema may compromise local blood flow or increase the brain's exposure to toxic substances that result in cytotoxic edema. Meanwhile, cytotoxic processes can predispose to vasogenic edema by involving the cells composing the blood-brain barrier or by precipitating inflammation-mediated blood-brain barrier injury. Although TBI, ischemic stroke, and liver failure were each historically believed to result in only one form of edema, modern literature demonstrates that each represents a mixture of vasogenic and cytotoxic edema.[1,2,6]

Hydrostatic cerebral edema results from displacement of CSF from the ventricular space into the brain interstitium; this occurs as a consequence of hydrocephalus when increased hydrostatic pressure pushes CSF through the ependymal lining. Radiographically, hydrostatic cerebral edema appears as CT hypoattenuation beneath the ependymal surface and tends to concentrate at the horns of the ventricles. Some, particularly older, literature will also use the term

hydrostatic cerebral edema to refer to edema in the context of severe hypertension; this is likely a conceptual oversimplification of hydrostatic pressure and does not account for the blood-brain barrier injury and cytotoxic injury that occurs with severe acute hypertension. Osmotic cerebral edema occurs when an osmotic gradient develops between the brain tissue and serum that favors entry of water into the brain. This form of cerebral edema may be underrecognized clinically, in part because it is called by a variety of other names, such as rebound edema (after rapid weaning of hyperosmolar therapy), water intoxication, or dialysis disequilibrium syndrome (after renal replacement therapy, particularly in patients with brain injuries).[7-9] **CASE 1-2** demonstrates the development of acute osmotic cerebral edema as a contributor to neurologic deterioration in a patient who was critically ill with severe liver failure.[8] Clinically significant osmotic cerebral edema most often occurs in the setting of concurrent vasogenic or cytotoxic cerebral edema because blood-brain barrier and astrocyte dysfunction result in reduced ability to regulate brain volume in the face of an osmotic challenge.[1] Osmotic cerebral edema may be difficult to appreciate on neuroimaging because the volume increase is distributed across the entire brain.[8] At this time, quantitative neuroimaging assessments of cerebral edema are not widely available clinically. However, research approaches are available to quantify cerebral edema using MRI and CT imaging techniques.[1,8,10]

INTRACRANIAL PRESSURE, CEREBRAL PERFUSION, AND BRAIN COMPRESSION

Conceptually, the intracranial compartment can be thought of as a rigid box (the skull) with a balloon attached to the side, which represents the anatomic reservoir where CSF and blood can be displaced from the skull. The rigid box has a fixed volume and contains three compartments: vascular blood, brain tissue, and CSF. This foundational concept is known as the Monro-Kellie doctrine. Pathologic processes result in an increased volume of these compartments or introduce space-occupying lesions that compress the other compartments (eg, a hematoma). As material is introduced into the box, some of the box's contents can be displaced to the balloon, which acts as a pressure buffer. At first, when the balloon is empty, the addition of material to the system results in only small increases in pressure. However, as the balloon becomes filled with displaced material, the same increase in volume results in progressively larger pressure increases. When the balloon is full, it takes on a rigid nature and additional volume in the system results in exponential pressure increases. The relationship between volume and pressure represented by progressively filling the balloon in this scenario describes the property of intracranial compliance. CSF, being lower in pressure than venous or arterial blood, functions as the primary buffer responsible for intracranial compliance; CSF can be displaced from the skull to the spinal cisterns and cranial nerve sheaths, which function as an intracranial compliance reserve to buffer ICP. To a lesser extent, compression of venous and then arterial structures with displacement of blood from the skull provides an additional compliance reserve; incidentally, displacement of arterial blood risks exacerbating brain injury through cerebral ischemia. Once intracranial compliance is exhausted, ICP increases exponentially. In patients with greater degrees of cerebral atrophy, as might occur with advanced age or chronic diseases such as cirrhosis, the ratio of CSF to brain is larger and, therefore, is a

KEY POINTS

- Cytotoxic edema results from derangements in cellular metabolism with resulting alterations in ionic gradients and movement of water into the brain tissue. Cytotoxic edema is classically associated with ischemic stroke and acute liver failure.
- Hydrostatic cerebral edema results from displacement of CSF from the ventricular space into the brain interstitium; this occurs as a consequence of hydrocephalus when hydrostatic pressure pushes CSF through the ependymal lining.
- Osmotic cerebral edema occurs when an acute osmotic gradient develops between the brain and serum favoring water entry into the brain. Patients with brain injuries receiving medical interventions that reduce serum osmolality, such as dialysis, are at particular risk for acute deterioration from this edema.
- Rapid identification and treatment of osmotic cerebral edema by returning serum osmolality to prior levels may be lifesaving.
- The intracranial compartment can be thought of as a rigid box with a balloon attached to the side. The balloon buffers volume added to the box and minimizes pressure increases until the balloon is full. The balloon represents intracranial compliance.

greater buffer against elevated ICP. The clinician should appreciate that monitoring ICP is insensitive to detecting cerebral edema (and other space-occupying pathology) before it progresses to severe levels because of intracranial compliance (FIGURE 1-5); failure to recognize this is, in part, responsible for the historical misperception that patients with hepatic encephalopathy from acute-on-chronic liver failure do not manifest cerebral edema.[1] It remains unknown whether cerebral edema that does not progress to elevated ICP (so-called low-grade cerebral edema) is benign. However, data

CASE 1-2

A 26-year-old man presented with fulminant liver failure from acetaminophen overdose. He developed hyperammonemia to 264 µmol/L, progressive encephalopathy, and cerebral edema on serial neuroimaging. He was started on hypertonic saline and was initiated on continuous renal replacement therapy with close serum osmolality monitoring to reduce ammonia levels while maintaining steady serum osmolality. The patient received a liver transplant on hospital day 6. Brain CT on hospital day 7 demonstrated improving cerebral edema (FIGURE 1-4A). On hospital day 8, the transplant abdominal incision could not be closed because of fluid overload. To address this, the patient was treated with a session of hemodialysis using sodium modeling (sodium concentration of dialysate decreases during hemodialysis session) rather than a constant isoosmolar sodium concentration dialysate. Three hours into the hemodialysis session, the patient was noted to have fixed dilated pupils and no longer withdrew from noxious stimulation. His serum osmolality had decreased from 354 mOsm/kg to 300 mOsm/kg. Emergent CT demonstrated worsened cerebral edema with brain volume increase of 35 mL (FIGURE 1-4B). The patient received 180 mL of 23.4% hypertonic saline over 90 minutes, with increase in serum osmolality to 348 mOsm/kg, after which his pupils were again briskly reactive and he withdrew from noxious stimulation. Repeat CT (FIGURE 1-4C) demonstrated brain volume reduction of 40 mL compared to the previous CT (FIGURE 1-4B). The patient was discharged to acute rehabilitation 2 weeks later. Six months later, the patient was living independently at home and working part-time.

from stroke and TBI suggest that cerebral edema, independent of elevated ICP, is a mechanism of secondary brain injury.[11-13]

In addition to clinical intuition from neuroimaging and neurologic examination, the status of intracranial compliance can be qualitatively assessed from the waveform recorded on invasive ICP monitors. With each heartbeat, a small bolus of arterial volume enters the skull; this process results in a characteristic waveform on the ICP monitor. The normal waveform has three peaks: P1 (cardiac systole), P2 (displaced intracranial contents meeting resistance

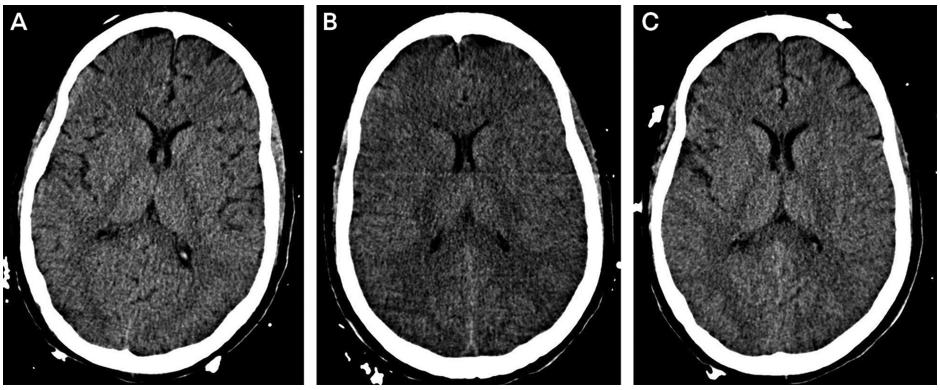

FIGURE 1-4

Imaging of the patient in CASE 1-2. Axial noncontrast head CT shows improving cerebral edema following liver transplantation (*A*), emergent CT imaging obtained after an acute neurologic deterioration the following day demonstrates worsened cerebral edema compared to the prior CT (*B*) and improved cerebral edema on repeat imaging after treatment with hypertonic saline (*C*). All three CT scans are shown with the same center: 42 width, 55 window. The greater cerebral edema of *panel B* can be visually appreciated by the brain's darker (hypodense) appearance.

COMMENT

Acute onset of cerebral edema and clinical brain herniation may occur in the setting of hemodialysis and preexisting brain injury. Although this scenario has been termed *dialysis disequilibrium syndrome*, this case illustrates an example of acute osmotic cerebral edema related to a rapid reduction in serum osmolality relative to brain osmolality. In addition to dialysis, medical interventions such as infusion of large volumes of hypotonic fluids and rapid weaning of osmotic agents may also lead to osmotic cerebral edema, particularly in patients with concurrent acute brain injury and other forms of cerebral edema. Measurement of serum osmolality is prudent in the patient with brain injuries with renal failure, liver failure, or shock because serum osmolality may be unexpectedly elevated. Hypertonic saline may be administered in these scenarios to ensure that reductions in serum osmolality are performed in a gradual manner and with close clinical monitoring. This case illustrates that severe neurologic deterioration from osmotic cerebral edema can be reversed with good patient outcome by rapidly recognizing the deterioration and acting to return serum osmolality to previous levels.

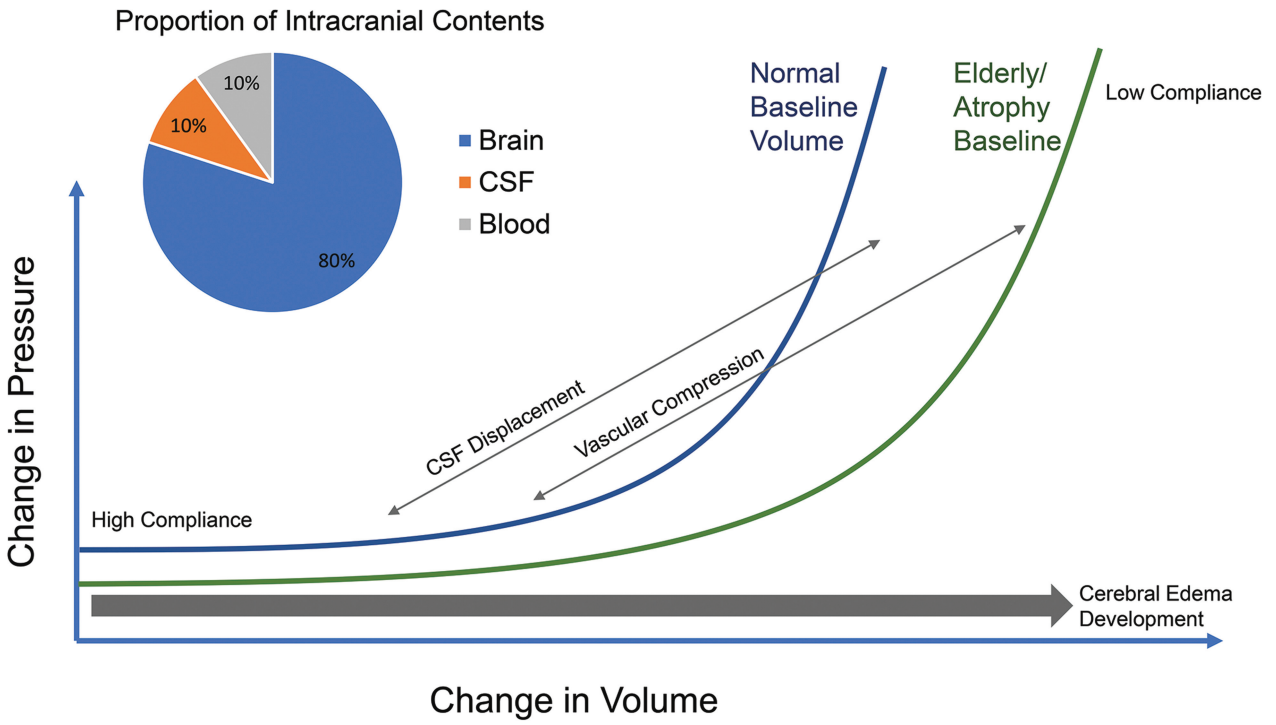

FIGURE 1-5

Intracranial compliance curves demonstrating the relationship between intracranial volume and pressure changes and compensatory mechanisms in patients with normal baseline brain volume and patients with baseline atrophy because of advanced age or chronic illness.

CSF = cerebrospinal fluid.

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from the structures that form the compliance reserve), and P3 (dicrotic wave from aortic valve closure). Normally, P1 is greater than P2, which is greater than P3. As compliance is initially compromised, P2 progressively becomes greater than P1. When compliance is more severely compromised, P1 and P2 begin to merge (FIGURE 1-6). These waveform changes can occur before the demonstration of ICP values that exceed the normal range (typical normal is 7 mm Hg to 15 mm Hg, with an upper limit of 20 mm Hg) and should suggest that elevated ICP may be detected in the near future. This waveform morphology should not be confused with ICP Lundberg waves. Lundberg waves (FIGURE 1-7) refer to intermittent nonsustained increases in ICP that are apparent when continuous ICP measurement is trended over minutes to hours.[14,15] Lundberg C waves are characterized by an ICP up to 25 mm Hg and pressure oscillations at 4 to 8 times per minute; Lundberg C waves may be seen in normal physiology and are likely due to cardiac and respiratory cycles. Lundberg B waves oscillate at 0.5 to 2 waves per minute over up to 5 minutes, and ICP is increased 20 mm Hg to 30 mm Hg above baseline; these waves are likely due to vasomotor instability when cerebral perfusion is compromised. Lundberg B waves are a sign of impaired intracranial compliance. Lundberg A waves (called *plateau waves*) are always pathologic and reflect critically exhausted intracranial compliance with elevated risk for brain herniation and death. Lundberg A waves are characterized by rapid increases in ICP from baseline to 50 mm Hg to 80 mm Hg; they typically last 5 to 20 minutes but may persist over hours. Lundberg A waves are believed to

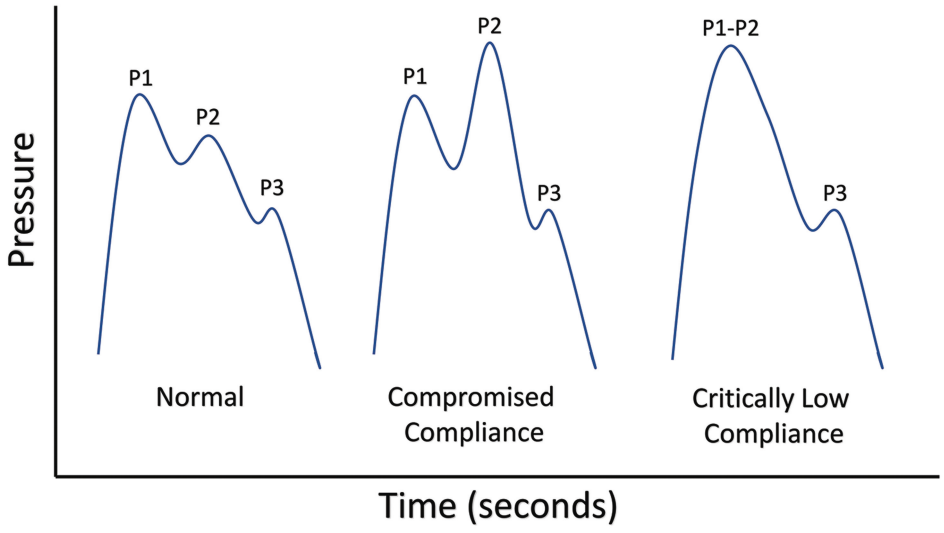

FIGURE 1-6
Intracranial pressure waveforms associated with individual heartbeats. Normal waveform shows P1 exceeds P2, which exceeds P3. With compromised intracranial compliance P2 exceeds P1. With critically low compliance, P1 and P2 merge.

KEY POINTS

- CSF functions as the primary buffer responsible for intracranial compliance. CSF can be displaced to the spinal cisterns and cranial nerve sheaths. Once intracranial compliance is exhausted, intracranial pressure increases exponentially.

- Lundberg A waves reflect critically exhausted intracranial compliance with elevated risk for brain herniation. Lundberg A waves are characterized by rapid increases in intracranial pressure to 50 mm Hg to 80 mm Hg lasting 5 to 20 minutes.

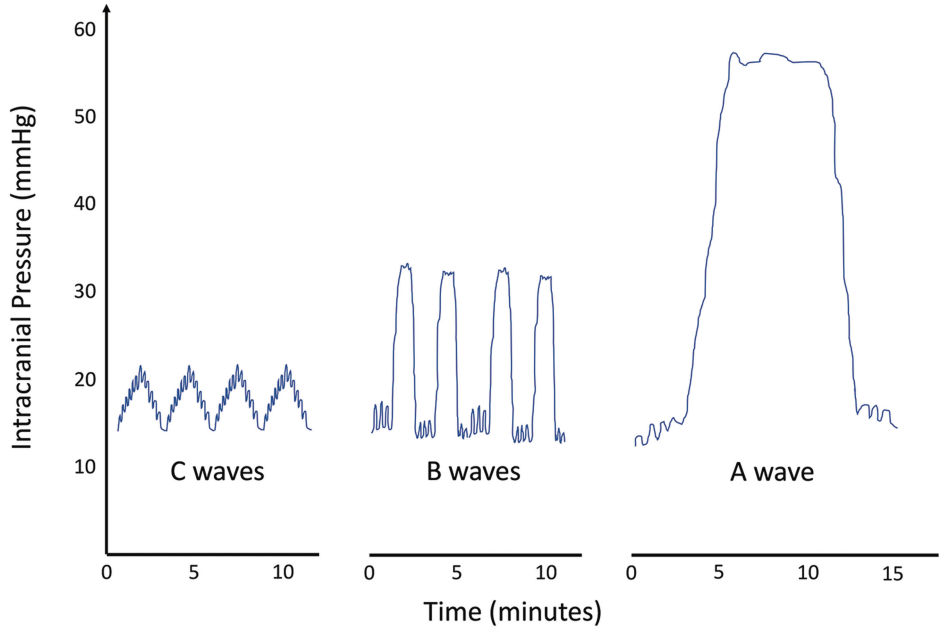

FIGURE 1-7
Lundberg intracranial pressure waves. C waves may be seen in normal physiology and are likely related to cardiac and respiratory cycles, and intracranial pressure (ICP) may increase to 25 mm Hg. B waves likely occur because of impaired cerebral perfusion and suggest impaired intracranial compliance. B waves occur as 0.5 to 2 waves per minute with ICP increasing 20 mm Hg to 30 mm Hg above baseline. A waves (also known as plateau waves) are rapid increases in ICP to 50 mm Hg to 80 mm Hg that typically last 5 to 20 minutes. A waves reflect critically exhausted intracranial compliance.

occur from cycles of cerebral vasodilation precipitated by episodes of reduced cerebral perfusion in the setting of greatly impaired compliance.[15] Although the occurrence of Lundberg A waves should trigger a rapid reassessment of available interventions, the transient self-resolving nature of Lundberg B and C waves suggests that not every ICP increase necessitates specific intervention. Treatment of every ICP increase over 20 mm Hg, however brief, would result in overtreatment and risk exposing the patient to treatment side effects with little benefit. The Brain Trauma Foundation guidelines recommend an ICP treatment threshold of 22 mm Hg, given that higher values are associated with increased mortality. Generally, ICP treatment algorithms reserve interventions for ICP above threshold for at least 10 minutes to avoid treating elevations that might resolve spontaneously.[16] The 22 mm Hg threshold is based on a population-level association between ICP above this threshold and mortality. An evolving literature suggests the possibility that optimal ICP thresholds may vary between patient subgroups, different time points after acute brain injury, and even within individual patients.[17]

Cerebral perfusion pressure (CPP) is a concept closely related to ICP. CPP is the pressure supplying arterial perfusion to the brain and is calculated by subtracting the ICP from the mean arterial blood pressure. Avoiding low CPP reduces the risk of secondary ischemic brain injury; however, the CPP calculation assumes that the pressure resisting vascular perfusion is equivalent throughout the cranium, which may not be the case in areas of focal brain compression. A long-standing therapeutic recommendation for CPP has been 50 mm Hg to 70 mm Hg, the normal CPP range.[18] However, the latest Brain Trauma Foundation guidelines recommended revising the CPP goal to 60 mm Hg to 70 mm Hg.[16] Although data from prior randomized studies failed to demonstrate a neurologic outcome difference between CPP thresholds of 50 mm Hg versus 70 mm Hg,[19] subsequent observational data suggested that patients who had any time with CPP below 50 mm Hg experienced a lower rate of survival than patients who had no time with CPP below 60 mm Hg.[16,20] Therefore, a wider margin against CPP below 50 mm Hg seems reasonable. These guidelines continue to advise against aggressive attempts to achieve CPP greater than 70 mm Hg, which has been associated with greater risk for acute respiratory distress syndrome (ARDS).[16] Numerous studies in the literature have taken opposing positions regarding whether ICP- or CPP-focused treatment algorithms are superior. No definitive study has supported one approach, and consensus guidelines recommend clinicians attend to both ICP and CPP goals.[16,18]

The normal brain is capable of regulating vasoconstriction and vasodilation to maintain a constant cerebral blood flow over a mean arterial blood pressure of about 50 mm Hg to 150 mm Hg through cerebral autoregulation.[21] Beyond the blood pressure bounds of cerebral autoregulation, cerebral blood flow becomes a passive pressure-dependent process. In the acute brain-injured state, it is possible for the normal physiologic responses of cerebral autoregulation to exacerbate injury. For example, during cerebral hypoperfusion, the normal physiologic response is cerebral vasodilation; however, in a patient with compromised intracranial compliance, the increased blood volume from vasodilation may lead to greater ICP elevation with subsequent decrease in CPP, which actually worsens cerebral ischemia. In this scenario, using vasopressors to augment CPP may allow vasoconstriction that reduces cerebral blood volume and leads to improved ICP and cerebral perfusion. However, excessive CPP could lead to

exacerbation of vasogenic edema in areas of blood-brain barrier dysfunction, which would increase brain volume and worsen ICP. Because of variable impairment of both global and regional cerebral autoregulation after acute brain injury,[21] the relationship between ICP, CPP, and cerebral blood volume can be complex and difficult to predict. These scenarios often require therapeutic trials to evaluate response. Although approaches exist to assess the integrity of cerebral autoregulation and estimate individualized optimal CPP goals,[21] these techniques remain unproven at a level to justify widespread use.

Currently the only way to determine ICP and CPP is through invasive measurement. The two most common ICP monitors are intraparenchymal sensors and external ventricular drains, (EVDs), which have the added benefit of being able to therapeutically drain CSF and are considered the gold standard ICP monitor. Noninvasive techniques, such as optic nerve sheath ultrasound and transcranial Doppler ultrasound, have been investigated as means of estimating ICP.[22,23] Although they may have utility in some scenarios, the confidence intervals for ICP estimates from noninvasive techniques remain too wide to substitute for invasive measurement.[22,23] Currently, ICP monitoring is not routine in the management of hemorrhagic or ischemic stroke, brain tumors, or meningitis, although intracerebral hemorrhage guidelines suggest ICP monitoring might be considered in patients who are comatose, those with evidence of herniation, or those with significant intraventricular hemorrhage or hydrocephalus.[18] There is a trend away from the use of ICP monitors in patients with acute liver failure because of concerns about hemorrhagic complications from monitor placement, observational data demonstrating no overall survival benefit, and an association with worse outcome in some subgroups.[8,24,25] However, ICP monitoring is routinely used in TBI. The Brain Trauma Foundation guidelines recommend ICP monitoring for patients who either have abnormal CT scans of the head and are comatose after resuscitation or have normal CT scans with two or more of the following: age older than 40 years, motor posturing, or systolic blood pressure below 90 mm Hg. This recommendation is based on a high incidence of elevated ICP in patients meeting these criteria (about 60%) rather than a proven mortality or neurologic outcome benefit from ICP monitoring.[16,26] In fact, the highest level evidence in this area, the BEST:TRIP (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure) trial, demonstrated no mortality, functional, or cognitive outcome difference between severe TBI management based on ICP monitoring compared to clinical assessments from physical examination and neuroimaging.[16,27] The clinical assessment group did have a significantly longer interval during which they received brain-specific treatments (median 4.8 days compared to 3.4 days), although this benefit required invasive monitor placement and ICP monitors carry a small but non-negligible risk of infection or hemorrhage.[27,28] The BEST:TRIP trial stirred controversy in the neurocritical care community because it was received by many in a polarized fashion: some cited it as a justification to abandon ICP monitoring all together, whereas others disregarded the results as having no generalizability outside the specific context in which the trial was conducted. In this author's opinion, an assessment of the BEST:TRIP trial that balances these viewpoints may be of greater utility in guiding the clinical application of ICP monitoring and future avenues of research. First, BEST:TRIP should not be used as a reason to abandon ICP monitoring given the large body of literature supporting clinical utility. On the other

KEY POINTS

- **The Brain Trauma Foundation recommends treatment for intracranial pressure greater than 22 mm Hg. Intracranial pressure should be elevated for about 10 minutes before treatment to avoid overtreatment of spontaneously resolving intracranial pressure elevations.**
- **Cerebral perfusion pressure is calculated by subtracting the intracranial pressure from the mean arterial blood pressure. The latest Brain Trauma Foundation guidelines recommended revising the cerebral perfusion pressure goal to 60 mm Hg to 70 mm Hg.**
- **Currently, intracranial pressure monitoring is not routine in the management of hemorrhagic or ischemic stroke, brain tumors, or meningitis but may be considered in select cases of coma, herniation, or hydrocephalus occurring in these diseases.**
- **Intracranial pressure monitoring should be considered in patients who are comatose after traumatic brain injury with abnormal CT scans of the head or normal CT scans with two or more of the following: age older than 40 years, motor posturing, or systolic blood pressure below 90 mm Hg.**

TABLE 1-1 **Brain Herniation Syndromes**[a,b]

Herniation syndrome	Mechanism	Notable clinical findings
Falcine	Supratentorial lesion; medial displacement of the cerebral hemisphere against the falx; cingulate gyrus displaced under the falx	Leg weakness; because of reduced likelihood of compression or displacement of the diencephalon, midbrain, or brainstem, mental status is less affected than in other herniation syndromes
Lateral diencephalon displacement	Supratentorial lesion; focal lesion that laterally displaces the diencephalon	Depressed consciousness proportionate to degree of displacement: 3-5 mm drowsy, 6-8 mm stupor, ≥9 mm coma; vertical gaze palsy if the dorsal midbrain is compressed; pituitary stalk avulsion with diabetes insipidus in severe cases[c]
Uncal transtentorial	Supratentorial lesion; unilateral medial temporal lobe (uncus) laterally displaced to compress ipsilateral cranial nerve III; midbrain directly compressed or laterally displaced	Enlarged sluggish pupil is an early sign, followed by ipsilateral fixed and dilated pupil, progressive cranial nerve III palsy, contralateral and/or ipsilateral hemiplegia, flexor or extensor posturing, and stupor/coma; ipsilateral hemiplegia is from midbrain displacement with contralateral cerebral peduncle compression against the Kernohan tentorial notch
Central-descending transtentorial	Supratentorial lesion; bilateral medial temporal lobe (uncus) laterally displaced or caudal displacement of supratentorium against diencephalon	Bilateral pupil dilation followed by cranial nerve III palsies if due to bilateral uncal herniation; if due to direct diencephalon compression, small minimally reactive pupils with roving eye movements giving way to midposition pupils; flexor followed by extensor posturing and stupor/coma
Rostrocaudal deterioration	Supratentorial lesion; downward displacement of the midbrain and pons	Signs of brainstem infarction secondary to shearing of medial perforating branches of the basilar artery, which is tethered to the circle of Willis
Upward-ascending transtentorial	Infratentorial lesion; upward displacement of cerebellum through tentorial incisura with dorsal midbrain compression, seen with combination of excessive supratentorial CSF diversion or robust hyperosmolar therapy and posterior fossa lesions that were not treated by surgical posterior fossa decompression	Vertical gaze palsy followed by stupor/coma; intracranial pressure monitor may report low intracranial pressure; cerebral aqueduct compression may result in acute hydrocephalus
Tonsillar	Infratentorial or severe supratentorial lesion; downward displacement of the cerebellar tonsils through the foramen magnum with cervicomedullary junction compression	Development of hydrocephalus, cranial nerve palsies, and stupor/coma from brainstem compression; quadriparesis from compression of medullary pyramids; Cushing reflex of hypertension, bradycardia, slow respirations; can progress to respiratory arrest

CSF = cerebrospinal fluid.

[a] Data from Posner JB, et al, Oxford University Press.[31]

[b] Irreversible injuries following brain herniation: Brain herniation may lead to compression of venous drainage with venous infarction and possible hemorrhagic conversion. Compression of arterial structures against dural reflections may lead to arterial infarcts, particularly compression of the posterior cerebral arteries during uncal or central herniation or compression of the anterior cerebral, pericallosal, or callosomarginal arteries during subfalcine herniation. Brain compression and displacement may also lead to shearing of penetrating arterioles, resulting in Duret hemorrhages, particularly seen in the brainstem.

[c] Brain herniation may result in diabetes insipidus because of injury to the hypothalamic-pituitary axis with loss of antidiuretic hormone expression. Diabetes insipidus results in the production of a large volume (>3 mL/kg/h for multiple hours) of dilute (specific gravity ≤1.005) urine that can result in severe hypovolemia and hypernatremia. Diabetes insipidus should be treated with volume resuscitation, administration of antidiuretic hormone, and discontinuation of hyperosmolar therapy to avoid exacerbation of hypernatremia.

extreme, this expertly designed and executed trial should not be disregarded through excessive criticism because it failed to confirm preconceived expectations. The unexpected results of the BEST:TRIP trial likely demonstrate that our knowledge of acute brain injury, cerebral edema, and ICP management remains incomplete. In addition, BEST:TRIP suggests that ICP monitoring is ultimately only a clinical tool and other approaches can be used to guide therapies to similar effect.

Before placing an ICP monitor or initiating therapy for cerebral edema, clinicians should first consider whether the mechanism of injury and available clinical data suggest that ICP elevations or secondary brain injury due to cerebral edema are likely to occur. In the case of ICP monitoring or obtaining serial neuroimaging, the clinician should consider how the information is likely to change management. Patients who are not comatose may not benefit from ICP monitoring or specific ICP-directed therapies and could be harmed by side effects. Patients with space-occupying injuries that are not severely distorting critical brain structures may only need supportive care and neurologic monitoring. Patients who are stuporous or comatose with possible diffuse cerebral edema, as can be seen in encephalitis or toxic-metabolic exposures (eg, liver failure, diabetic ketoacidosis, or toxic leukoencephalopathies), may represent a challenging decision because diffuse edema can be hard to appreciate visually until it is severe; assessing the response to a trial of hyperosmolar therapy may be helpful in such patients.[8,29] On the other hand, a normal ICP value should not be comforting when in conflict with other concerning clinical data, such as an unexplained deterioration of the neurologic examination or radiographic progression of brain distortion. The intracranial space is not a perfect sphere filled with a homogeneous fluid, and the brain does not behave as a newtonian fluid.[30] Furthermore, the dural reflections and bony curvature of the middle cranial fossa can facilitate the creation of pressure gradients within the skull. In fact, pressure gradients of 30 mm Hg have been recorded between the middle and posterior fossae, and gradients of 20 mm Hg have been recorded between the ventricular fluid and the posterior fossa.[30] Even EVDs may fail to detect significant pressure gradients, especially if focal lesions prevent the free communication of CSF. Brain herniation, the displacement of brain structures into adjacent cranial compartments with compression of those compartments and structural brain distortion, can occur as a result of these pressure gradients (**TABLE 1-1**).[31] Life-threatening brain herniation may occur even if an ICP monitor reports a normal pressure. Therefore, monitoring for brain herniation is dependent on serial neurologic examinations and potentially serial neuroimaging.

Numerous monitoring technologies have been used for acute brain injury, such as cerebral microdialysis, near-infrared spectroscopy, automated pupillometry, and brain tissue oxygenation. Although ample literature may be available to justify the use of these technologies in institutional management protocols, most of these technologies lack sufficient evidence to advocate for their widespread standardized use.[32] The BOOST3 (Brain Oxygen Optimization in Severe TBI, Phase 3) trial is currently investigating the efficacy of ICP plus brain tissue oxygen monitoring compared to ICP monitoring alone in TBI.[33] The trial has attracted enthusiasm, and BOOST2 (Brain Tissue Oxygen Monitoring in Traumatic Brain Injury [TBI]) provided promising preliminary data in favor of brain tissue oxygenation monitoring,[34] although cautious interpretation is warranted given that the ICP monitoring–only group had significantly more frequent severe brain compression.[35]

KEY POINTS

- **Although intracranial pressure monitoring does not have a proven outcome benefit, it still has considerable clinical utility. However, clinicians could also consider alternative strategies, including clinical assessment and serial neuroimaging.**
- **Normal intracranial pressure values should not be comforting when in conflict with other concerning clinical data. Significant pressure gradients may exist in the skull, and brain herniation can occur with normal intracranial pressure monitor readings.**

TREATMENT OF CEREBRAL EDEMA, BRAIN COMPRESSION, AND ELEVATED INTRACRANIAL PRESSURE

In the patient presenting with an acute brain injury, the treatment of cerebral edema, brain compression (by diffuse or focal processes), and elevated ICP should begin with establishing an understanding of the severity and likely trajectory of the injury based on history, mechanism, physical examination, and review of emergent neuroimaging. This will suggest the pace at which interventions may need to be introduced and allow preparations to be made if the need for high-tier interventions seems likely. All patients with acute brain injury

TABLE 1-2 **Tiers of Intracranial Pressure and Cerebral Edema–Directed Therapies[a]**

Tier	Therapies
Zero, standard measures for all patients at risk of intracranial pressure elevation	Supportive medical care (airway, breathing, circulation)
	Analgesia for comfort
	Sedation to tolerate medical interventions (Richmond Agitation and Sedation Scale score 0 to -2)[37]
	Avoid fever (normothermia 36 °C to 37 °C [96.8 °F to 98.6 °F])
	Avoid constipation/abdominal distension
	Head at 30- to 45-degree elevation
	Head midline; avoid jugular vein compression
	Isotonic or hyperosmolar fluids targeting normal serum sodium (>135 mmol/L)
	Steroids for select conditions[b]
One	Mannitol or hypertonic saline for symptom-directed or osmolality/sodium level goal
	CSF diversion, drain 5-10 mL if external ventricular drain in place
	Selective consideration of surgical decompression or lesion resection
	Mild hyperventilation[c]
Two	Hypertonic saline if refractory to mannitol; consider higher osmolality goal
	Sedation and analgesia for deeper Richmond Agitation and Sedation Scale goal
	Reconsider surgical decompression as lifesaving measure
	Mild hyperventilation[c]
Three	Patient determined not to be a surgical candidate
	Sedation/barbiturate titrated to intracranial pressure goal or EEG burst suppression
	Moderate hypothermia (core temperature 32 °C to 34 °C [89.6 °F to 93.2 °F])
	Moderate hyperventilation[d]

CSF = cerebrospinal fluid; EEG = electroencephalogram.
[a] Data from Venkatasubramanian C, et al, Neurocrit Care.[36]
[b] Brain tumors, cerebral abscess, meningitis, neuroinflammatory conditions (eg, acute demyelinating encephalomyelitis [ADEM]).
[c] As a temporizing measure ($Paco_2$ 30 mm Hg to 35 mm Hg or 5 mm Hg below baseline); wean after use.
[d] As temporizing measure ($Paco_2$ 25 mm Hg to 35 mm Hg or 10 mm Hg below baseline); wean after use.

should first receive systemic resuscitation (airway, breathing, circulation) and supportive medical care followed by standard ICP-directed measures (tier zero interventions), as discussed below. It is vital for neurologists to be aware of and advocate for the correction of systemic physiologic derangements because conditions such as shock or severe metabolic disturbance can contribute to secondary brain injury. Possible indications for early surgical intervention should be identified, and then multidisciplinary discussions should delineate potential surgical versus medical treatment options. ICP-targeted (and cerebral edema/compression-targeted) therapy should follow a tiered approach (TABLE 1-2[36,37]), in which therapies from higher tiers are introduced after ensuring optimization of lower-tier interventions. Institutional treatment algorithms improve the consistency of care and patient outcomes,[38] and ideally these algorithms should be developed and regularly reviewed by a multidisciplinary team. Many example algorithms are available from clinical trials or professional societies that may be adapted to individual institutional settings.[27,39]

Clinical brain herniation (TABLE 1-1) and severe or sustained elevation of intracranial pressure represent neurologic emergencies that should be treated with the same urgency afforded to a cardiac code situation. Although brain herniation often contributes to death or severe disability, it is possible for patients to have an acceptable functional outcome after brain herniation if effective interventions are rapidly implemented (CASE 1-2). Rapid initiation of empiric interventions to improve intracranial compliance, such as acute hyperosmolar therapy and hyperventilation (discussed further below), are indicated in an attempt to reverse the brain herniation. Efforts to identify the precipitating factors leading to brain herniation should be initiated concurrently with empiric therapeutic interventions. In some cases, recent clinical events may suggest a possible precipitant; for example, brain herniation could be precipitated by an acute decline in serum osmolality associated with initiating renal dialysis or administering hypotonic fluids, dysfunction of an EVD, or even fever in patients with severely compromised intracranial compliance. Emergent neuroimaging should also be pursued to identify structural causes of brain herniation that could justify surgical intervention. A clinician should accompany the patient in transport to emergent neuroimaging to continue directing attempts at reversing the brain herniation.

Supportive Medical Care and Standard Intracranial Pressure–Directed Measures (Tier Zero)

Systemic resuscitation and goal-directed supportive medical care are critical to avoid secondary brain injury. Numerous studies have demonstrated that hypotensive and hypoxic episodes are associated with worse outcome in patients with TBI; in fact, TBI guidelines recently emphasized this point by revising systolic blood pressure goals from greater than 90 mm Hg to greater than 100 mm Hg for patients 50 to 69 years of age and 110 mm Hg for patients 15 to 49 and older than 70 years of age.[16] On the other hand, excessive hypertension could contribute to hematoma expansion or vasogenic edema in patients with acute brain injury. In addition, all patients at risk for cerebral edema and increased ICP should be treated with tier zero interventions (TABLE 1-2). These interventions are aimed at optimizing intracranial compliance and avoiding ICP exacerbation. Elevating the head of bed to 30 degrees and avoiding jugular vein compression

KEY POINTS

- **Intracranial pressure–targeted therapy should follow a tiered approach in which therapies from higher tiers are introduced after ensuring optimization of lower-tier interventions.**
- **Systemic resuscitation and goal-directed supportive medical care are critical to avoid secondary brain injury. Numerous studies have demonstrated that hypotensive and hypoxic episodes are associated with worse outcome.**

from causes such as neck rotation or tight cervical collars facilitates venous drainage. Severe constipation and other causes of abdominal distension can raise abdominal pressure and oppose the displacement of CSF to the lumbar cistern; in patients with traumatic injury or shock, unrecognized intraabdominal hypertension can contribute to elevated ICP. Even small intracranial volume changes induced by untreated pain, agitation, and fever could lead to elevated ICP in the patient with compromised intracranial compliance.

Selective Corticosteroids (Tier Zero)

Corticosteroids are most commonly used to treat vasogenic edema resulting from intraaxial or extraaxial brain tumors. Corticosteroids are believed to improve tumor-induced blood-brain barrier permeability through upregulation of tight junction proteins and inhibition of cytokine-induced blood-brain barrier disruption.[40] Because of their numerous side effects, steroids should be reserved for the treatment of significant symptoms that are referrable to the peritumoral edema rather than the tumor itself. For acute edema treatment, 10 mg to 20 mg IV dexamethasone may be administered, followed by maintenance doses of 4 mg/d to 24 mg/d, given orally or intravenously; it is common practice to divide the maintenance dose 4 times daily, although twice-daily dosing is acceptable practice.[40,41] The clinician should monitor for adverse effects such as hyperglycemia, gastric distress, and adrenal insufficiency with corticosteroid weaning, and the lowest effective dose of steroids should be used to minimize these adverse effects.[41] It has classically been taught that steroids should be withheld before biopsy of new tumors because steroids may reduce the diagnostic yield for lymphoma; however, recent studies suggest this is infrequently the case.[42] Dexamethasone may be tapered over weeks following surgical or radiation tumor therapy; however, in palliative situations, dexamethasone doses may need to be increased to address neurologic symptoms from progressive edema. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has relatively recently begun to be used for symptomatic peritumoral edema refractory to steroids[40]; the effect begins within a few days, which limits bevacizumab's utility in the acute setting, and a poorly defined risk of intracerebral hemorrhage exists.

The role of corticosteroids for treating vasogenic edema from cerebral abscesses or meningitis is less clear. For abscesses, steroids are generally reserved for severe cases of edema because of concerns that steroids might reduce antibiotic penetration or increase the risk of intraventricular rupture of periventricular abscesses.[43] In meningitis, multiple lines of evidence have suggested neurologic (principally reduced hearing loss) and possible mortality benefits from corticosteroids, especially in some subgroups such as in patients with *Streptococcus pneumoniae* meningitis.[44] In contrast, the CRASH (Corticosteroid Randomisation After Significant Head Injury) trial demonstrated that patients with severe TBI treated with 48 hours of methylprednisolone had significantly increased mortality. As such, steroids are contraindicated in the treatment of TBI.[16,45] Steroids are not used in the management of cerebral edema from hemorrhagic or ischemic stroke because current evidence suggests no benefit and potential harm.[44,46]

Osmotic Therapy (Tiers One and Two)

Mannitol and hypertonic saline are the main osmotic agents used to treat cerebral edema and work primarily by generating an osmolar gradient between the brain

and plasma. Hypertonic saline is available in concentrations ranging from 2% to 23.4% and may be given by bolus or continuous infusion. For bolus dosing, 150 mL to 500 mL of 3% saline over 15 to 30 minutes or 30 mL of 23.4% saline over 10 minutes is common; faster administration of 23.4% saline risks acute right heart failure from fluid overload. Concentrations lower than 7.5% saline can be given by peripheral lines in a large vessel with close monitoring to avoid vascular injury and tissue necrosis by extravasation. Although central venous access is preferred for saline concentrations of 7.5% or more, 23.4% boluses by intraosseous cannulation (placing a sturdy needle through cortical bone into the medullary cavity of a bone for medication infusion, often using a power motor drill to facilitate insertion) can be considered in life-threatening circumstances in which establishing central venous access would cause delay; transient self-resolving hypotension can occur in about one-fourth of 23.4% saline boluses given by intraosseous cannula infusion compared to 8% to 17% of 23.4% saline boluses given by central venous catheter infusion.[47] Typical guidance is to avoid serum sodium greater than 160 mmol/L; however, this advice is not based on high-quality data and individual risks and benefits should be considered.[44] Targeting serum sodium up to 170 mmol/L in many patients with diffuse cerebral edema from liver failure has resulted in good neurologic outcomes in select cases.[8,29] Hypertonic saline may produce hyperchloremic metabolic acidosis and appears to increase the risk of acute kidney injury when serum sodium approaches 160 mmol/L or serum chloride approaches 115 mmol/L[44]; use of hypertonic saline buffered in acetate might reduce this risk.

Mannitol is an osmotic diuretic that is delivered by a filtered peripheral IV catheter as a 20% solution at a bolus dose of 0.5 g/kg to 2 g/kg, depending on the severity of the indication. Mannitol is typically redosed as boluses every 4 to 6 hours guided by serum osmolality measurements. Practice has shifted away from continuous mannitol infusion because a small portion (approximately 10%) of mannitol appears to leak across the blood-brain barrier, which may create an increased risk for rebound edema when mannitol therapy is weaned after continuous or prolonged use. Typical guidance is to avoid serum osmolality greater than 320 mOsm/kg or an osmolar gap (measured minus calculated osmolality) greater than 20 mOsm/kg. This guidance is largely based on classic teachings that exceeding these thresholds increases the risk of acute kidney injury, but a 2020 guideline statement was unable to identify evidence to support these thresholds.[44] Since hypovolemia and renal failure are risks of mannitol therapy, the clinician should monitor for these complications but may decide that cautiously exceeding the classic thresholds is beneficial. Additionally, the strong diuretic effect of mannitol is frequently underappreciated by those less familiar with its use. When transferring patients from remote emergency departments, concurrent saline infusion should be considered if mannitol therapy is given before transport to prevent dramatic hypovolemia from mannitol-induced diuresis. However, both mannitol and hypertonic saline appear to be effective in treating elevated ICP in patients with anuric end-stage renal disease, suggesting neither therapy requires diuresis to be effective.[48] In addition, the serum osmolar gap does correlate with mannitol levels such that a large gap likely indicates that mannitol is still present and therapeutically active; monitoring the osmolar gap may inform the clinician whether or not to redose mannitol. Since mannitol is primarily eliminated by urinary excretion but is cleared by hemodialysis, the clinician should expect mannitol to have a delayed elimination in patients with

KEY POINTS

- **Because of their numerous side effects, steroids should be reserved for the treatment of significant symptoms that are referrable to peritumoral edema rather than the tumor itself.**
- **Steroids are contraindicated in the treatment of traumatic brain injury because of increased mortality.**

renal failure pending receipt of renal replacement therapy, which should be initiated with caution to avoid rapid osmolar shifts and exacerbation of ICP.

The selection of osmotic agent for the individual patient is most often based on practitioner preference and the patient's volume status, with hypertonic saline used for those needing volume expansion and mannitol used for those needing diuresis. In urgent situations, the osmotic agent should be dictated by availability and familiarity at the treating institution. Many emergency departments do not stock and are not familiar with hypertonic saline but are familiar with mannitol. No high-quality evidence indicates that either hypertonic saline or mannitol improves mortality or neurologic outcome or that one agent is superior to the other agent.[44] However, a body of literature suggests that hypertonic saline may have quicker onset and more durable ICP reduction and may be effective when mannitol has failed.[44] This literature likely explains a general trend toward greater use of hypertonic saline. Furthermore, Koenig and colleagues[49] reported that 23.4% hypertonic saline boluses could clinically reverse transtentorial herniation, an effect more frequent when serum sodium increased greater than 5 mmol/L. However, the reversal of cerebral herniation is likely not a threshold effect and may differ between underlying disease states; this article author's group observed that volumetric cerebral edema reduction was linearly related to acute osmolality increase in a cohort with severe hepatic encephalopathy.[8,29] Incidentally, the magnitude of cerebral edema reduction affected by aggressive osmotic therapy is small; approximately 15 mL of cerebral edema reduction was sufficient to meaningfully improve neurologic examination scores in this cohort, consistent with the exponential nature of intracranial compliance during severe cerebral edema.[8,29]

Osmotic therapy should be reserved for symptomatic clinical deterioration that is likely to benefit from improved intracranial compliance and should not be used prophylactically. In fact, prophylactic mannitol has been associated with harm.[44] The primary utility of osmotic therapy is to temporize intracranial compliance until more definitive therapy occurs, such as surgical intervention, or until enough time has passed that cerebral edema begins to abate. It has long been recognized that the brain's astrocytes begin to accumulate idiogenic osmoles (such as amino acids, polyols, and methylamines) to reequilibrate brain-plasma osmolality and normalize brain volume in response to osmotic therapy.[50] More recent literature suggests that premature osmotic therapy could actually predispose to greater cerebral edema formation in patients who are vulnerable through increased blood-brain barrier permeability and upregulation of aquaporin-4 (AQP4) water channel expression on astrocyte end feet.[51] Consistent with this hypothesis, this article author's group recently observed that spontaneous hyperosmolality at hospitalization for severe liver failure was strongly associated with encephalopathy severity and altered CSF composition.[51] Therefore, initiating osmotic therapy before it is needed for intracranial compliance may actually promote an earlier development and greater magnitude of edema through increased blood-brain barrier permeability; this may ultimately obligate clinicians to maintain a higher osmolality later in the disease course than might otherwise be needed.

The ideal approach to initiating and escalating osmotic therapy is debatable, without strong evidence favoring one approach.[44] Therapy might be titrated to clinical symptoms or to a serum sodium or osmolality goal and accomplished by bolus dosing of mannitol or hypertonic saline with or without continuous hypertonic saline infusion. Bolus therapy to achieve a symptomatic goal and then

maintaining serum osmolality with continuous 3% saline infusion (0.5 mL/kg/h to 1 mL/kg/h) along with serial sodium and osmolality measurements is one approach; this might avoid rebound osmotic edema because of decline in serum osmolality between boluses concurrent with accumulation of brain idiogenic osmoles.

CSF Diversion and Decompressive Surgery (Tiers One and Two)

In patients with symptomatic hydrocephalus, CSF diversion is a first-line therapy. However, in cases of complex brain injury mechanisms, the contribution of hydrocephalus to the clinical presentation is not always clear and practitioners may have differing opinions on neuroimaging findings. In these cases, a multidisciplinary discussion may be helpful. CSF diversion by an EVD, without concurrent surgical decompression of the posterior fossa, should be avoided as the sole therapy in patients with hydrocephalus from compressive lesions in the posterior fossa because of the risk of upward herniation.[18]

Surgical intervention may be considered as a tier one therapy in select patients with impaired intracranial compliance because of focal compressive lesions. For example, in patients 60 years of age and younger with malignant middle cerebral artery infarcts who neurologically deteriorate despite medical therapy, decompressive craniectomy within 48 hours of stroke is recommended to improve mortality and functional outcome.[52] Patients older than 60 years of age with similar malignant infarcts appear to have a mortality but not functional outcome benefit from early decompressive craniectomy. In patients with posterior fossa lesions causing brainstem compression or obstructive hydrocephalus, posterior fossa decompression is considered first-line therapy.[18] In contrast, decompressive craniectomy with or without hematoma evacuation has not proved to improve functional outcomes in patients with supratentorial intracerebral hemorrhage and is currently considered a lifesaving measure when patients deteriorate despite medical management.[18]

In patients with impaired intracranial compliance because of multifocal brain injuries such as severe TBI, decompressive craniectomy is a tier two measure based on data from the DECRA (Early Decompressive Craniectomy in Patients With Severe Traumatic Brain Injury) and RESCUEicp (Randomised Evaluation of Surgery With Craniectomy for Uncontrollable Elevation of Intracranial Pressure) clinical trials. DECRA found that early bifrontal decompressive craniectomy in severe TBI resulted in improved ICP but worse neurologic outcome compared to standard care.[53] A criticism of DECRA was that patients were randomly assigned before ICP had proved to be sufficiently refractory to medical therapy, and the trial essentially investigated surgical intervention as tier one therapy. RESCUEicp required ICP to be higher and for a more prolonged period before randomization, testing decompressive craniectomy as a tier two intervention. RESCUEicp demonstrated improved survival from decompressive craniectomy and higher rates of severe disability and vegetative state compared to continued medical therapy but noted no improvement in the rate of good outcome.[54] DECRA and RESCUEicp suggest that for diffuse brain injury, decompressive craniectomy is a tier two option that can improve survival, but decision makers should understand the expected outcome is for most survivors to face severe disability.

Minimally invasive surgical techniques currently in development may have implications for ICP management in select diseases (CASE 1-3). The 2019

KEY POINTS

- In urgent situations, the osmotic agent used to treat cerebral edema or elevated intracranial pressure should be dictated by availability and familiarity. Many emergency departments do not stock and are not familiar with hypertonic saline but are familiar with mannitol.
- Osmotic therapy should be reserved for patients with cerebral edema or elevated intracranial pressure and with symptomatic clinical deterioration that is likely to benefit from improved intracranial compliance and should not be used prophylactically.
- Initiating osmotic therapy before it is needed for intracranial compliance may actually promote an earlier development and greater magnitude of edema through increased blood-brain barrier permeability; this may ultimately obligate clinicians to maintain a higher osmolality later in the disease course than might otherwise be needed.
- In patients 60 years of age and younger with malignant middle cerebral artery infarcts who neurologically deteriorate despite medical therapy, decompressive craniectomy within 48 hours of stroke is recommended to improve mortality and functional outcome.
- In patients with posterior fossa lesions causing brainstem compression or obstructive hydrocephalus, posterior fossa decompression is considered first-line therapy.

CASE 1-3

A 62-year-old man with a history of moyamoya syndrome, remote right middle cerebral artery watershed infarct, and left external carotid to internal carotid artery bypass surgery 1 month prior presented with acute onset of headache, right-sided hemiplegia, and lethargy. Head CT (FIGURE 1-8A) showed a large left lobar hemorrhage with brain compression. Hypertonic saline was initiated for symptomatic brain compression, and serum sodium was increased to 155 mmol/L. The patient was taken for urgent hematoma evacuation by minimally invasive endoscopic approach, which succeeded in removing the majority of the hematoma (FIGURE 1-8B). The patient returned to the intensive care unit with modest improvement in lethargy. Hypertonic saline infusion was discontinued with the expectation that intracranial compliance had sufficiently improved.

The following morning the patient was noted to be stuporous, and his serum sodium was 150 mmol/L. Repeat head CT showed worsened cerebral edema and brain compression comparable in severity to his preoperative neuroimaging (FIGURE 1-8C). The patient clinically improved after increasing serum sodium to 157 mmol/L but ultimately progressed to brain death 4 days later.

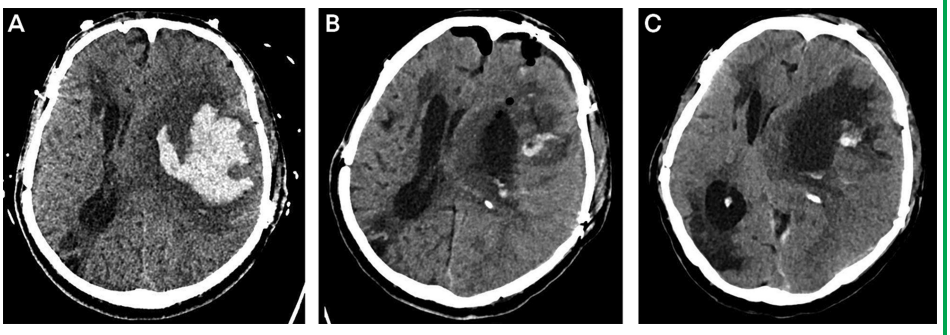

FIGURE 1-8
Imaging of the patient in CASE 1-3. Axial head CT shows a large left lobar hemorrhage with brain compression (*A*), the majority of which was removed through a minimally invasive endoscopic approach (*B*). Repeat imaging the following day shows worsened edema and brain compression comparable in severity to preoperative imaging (*C*).

COMMENT

This case illustrates the use of minimally invasive endoscopic evacuation of a hematoma in an attempt to improve intracranial compliance. The series of CT scans illustrates that brain compression did improve after hematoma evacuation, but considerable brain compression remained and the hematoma cavity failed to collapse. Ultimately, intracranial compliance was not improved enough to allow reduction in osmotic therapies, and, in fact, cerebral edema and brain compression progressed despite hematoma evacuation. This case illustrates that although minimally invasive surgical procedures are becoming more common for acute brain injury, they are not a panacea; close monitoring and intensive medical interventions will remain critical.

MISTIE-III (Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III) trial investigated whether evacuation of supratentorial intracerebral hemorrhage using a minimally invasive catheter approach could improve outcome compared to standard care.[55] MISTIE-III demonstrated improved survival in the surgical arm but did not demonstrate improved functional outcome. However, the technique appeared to reduce brain compression and, in the subgroup with more technically successful hematoma evacuations, appeared to have a potential functional outcome benefit. MISTIE-III has stimulated interest in a variety of minimally invasive hematoma evacuation techniques that could have implications for improving intracranial compliance by reducing hematoma volume.

KEY POINT

- Therapeutic hypothermia may be used for refractory intracranial pressure elevation, but prophylactic hypothermia does not improve outcome in severe traumatic brain injury and might be harmful.

Anesthetics for Metabolic Suppression (Tiers Two and Three)

Anesthetics can be used for cerebral metabolic suppression, which will reduce cerebral blood volume and improve ICP while maintaining adequate oxygenation. Increasing sedation with propofol or benzodiazepines can be used as a tier two ICP approach. For refractory ICP elevation, pentobarbital is the mainstay approach. Although strong evidence suggests that pentobarbital effectively lowers ICP, no high-quality evidence has proven that pentobarbital improves patient outcomes.[16] Pentobarbital may be started as a 5 mg/kg to 15 mg/kg infusion over 30 to 120 minutes followed by maintenance infusion of 1 mg/kg/h to 4 mg/kg/h.[36] Pentobarbital is then titrated to ICP goals and continuous EEG of at least 50% suppression. The doses of barbiturate in these infusions can cause cardiac suppression and vasoplegia, requiring vasopressor support, and can also cause paralytic ileus, immunosuppression, and bone marrow suppression. IV pentobarbital and phenobarbital include propylene glycol; thus, the osmolar gap should be monitored since propylene glycol accumulation can lead to severe lactic acidosis, acute renal failure, and shock. High-dose barbiturates can suppress brainstem function, including pupillary function, and mimic brain death. Since pentobarbital can take days to clear (half-life 15 to 50 hours), caution should be exercised during prognostication. Weaning pentobarbital can be fraught with both withdrawal seizures and ICP elevation recurrence, particularly if weaning is done too rapidly. Phenobarbital can be started to facilitate pentobarbital weaning and allow long-term barbiturate weaning and should be considered in advance when anticipating prolonged weaning periods.

Induced Hypothermia (Tier Three)

Hypothermia to 32 °C to 34 °C (89.6 °F to 93.2 °F) has been shown to be effective for refractory ICP elevation but has not demonstrated improved patient outcomes.[16] In 2015, the results from the Eurotherm3235 (European Study of Therapeutic Hypothermia [32-35 °C] for Intracranial Pressure Reduction After Traumatic Brain Injury) trial demonstrated that early initiation of hypothermia for ICP control after TBI was associated with worse functional outcome and greater mortality than standard care, despite the need for fewer medical ICP-directed interventions. The POLAR-RCT (Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury-Randomized Clinical Trial) reported results in 2018 and demonstrated no difference in neurologic outcome or mortality between prehospital initiation of prophylactic hypothermia and standard care with normothermia; interestingly, prophylactic hypothermia did not lead to

lower ICP and was associated with more frequent pneumonia.[56] Nevertheless, hypothermia remains a tier three option for refractory ICP. Hypothermia is typically achieved with surface or intravascular cooling devices. An antishivering protocol is needed because shivering prevents effective temperature management and can increase cerebral metabolism and systemic hypercarbia, which leads to counterproductive ICP elevation. Antishivering interventions include surface counterwarming (heated air blankets on the arms and legs), magnesium, buspirone, meperidine, sedatives, and paralytic medications. Therapeutic hypothermia requires close monitoring of electrolytes and cardiovascular status. During induction, severe hypokalemia, significant diuresis, and skin necrosis (due to peripheral vasoconstriction and pressure from external cooling pads) may occur. Rewarming should occur slowly (≤0.1 °C [0.18 °F] per hour) with close monitoring because of rebound hyperkalemia and potential distributive shock from peripheral vasodilation.

Hyperventilation (Tiers One Through Three Transient Rescue Therapy)

Hyperventilation can be very effective at reducing ICP, but its utility as a management strategy is limited.[44] Hyperventilation reduces ICP by causing cerebral vasoconstriction. In patients experiencing an ICP crisis, cerebral vasoconstriction can contribute to cerebral ischemia, which may then contribute to further cerebral edema and impairment of intracranial compliance. As such, hyperventilation should primarily be used as a transient emergency intervention to bridge a patient to a more definitive therapy. Furthermore, the benefits of hyperventilation are expected to be time limited because the brain will eventually buffer the pH change induced by hyperventilation and the cerebral vascular caliber will return to baseline. Hyperventilation $PaCO_2$ targets of 25 mm Hg to 35 mm Hg are typically suggested; however, this guidance does not account for patients who may have chronic carbon dioxide retention from pulmonary disease. Hyperventilation should be gradually weaned after it is used because a sudden increase in $PaCO_2$ will lead to an acute increase in cerebral blood volume, which could precipitate ICP elevation.

THE GLYMPHATIC SYSTEM AND CELLULAR TARGETS FOR CEREBRAL EDEMA TREATMENT

The discovery of the brain's glymphatic (glial-lymphatic) system (**FIGURE 1-9**[57]) and meningeal lymphatic vessels in the past decade represents potential therapeutic implications for a number of neurologic disorders, including acute brain injury and cerebral edema.[58-60] The glymphatic system consists of perivascular spaces through which CSF flows in to the brain, driven by the pulsations of the arterial wall.[61] CSF exits these perivascular spaces into the brain parenchyma in a process facilitated by AQP4 water channels on astrocyte end feet.[62] Within the brain parenchyma, the CSF mixes with interstitial fluid and fluid that influxes across the blood-brain barrier and moves by bulk flow through the brain to be collected in perivascular spaces around venules. This process appears to be responsible for the clearance of waste products, including amyloid-β, and may also be involved in distributing metabolites and signaling molecules through the brain.[58] Furthermore, the rate of fluid flow through the glymphatic system appears to be under circadian control and is further upregulated by sleep or anesthesia. When the glymphatic system is downregulated while awake, a greater portion of CSF appears to drain directly to meningeal and cervical

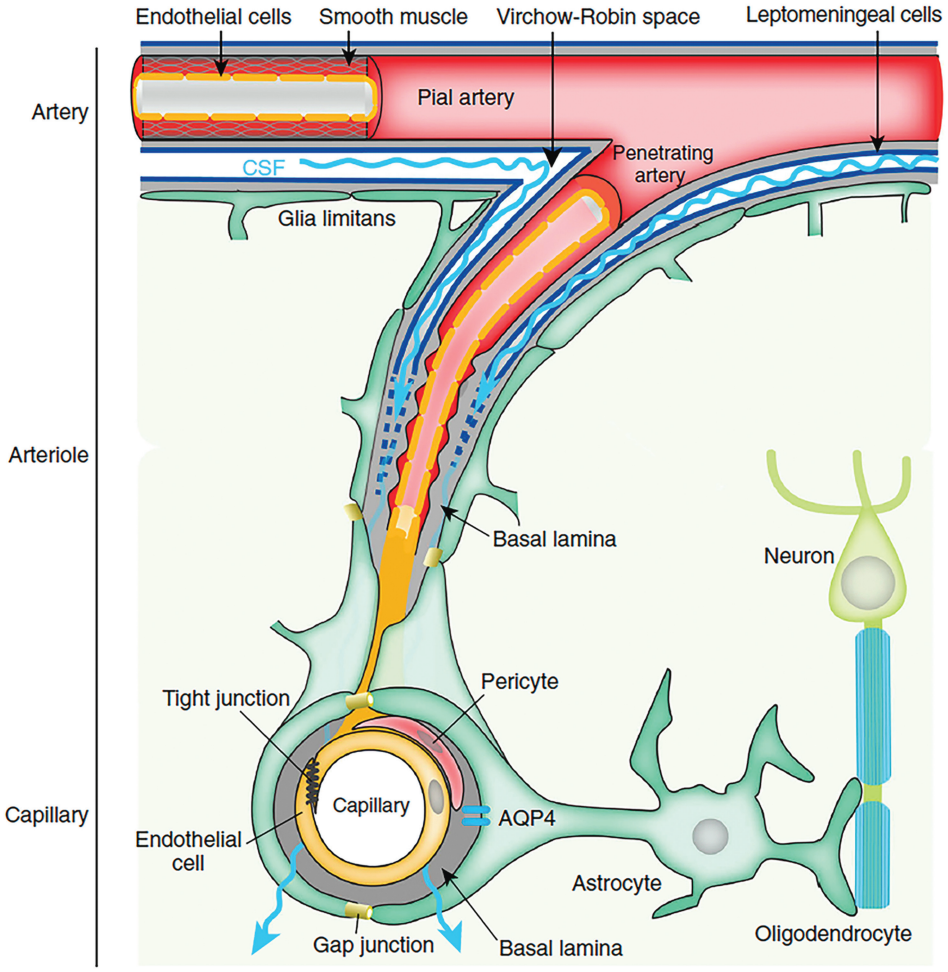

FIGURE 1-9

The glymphatic system. Pial arteries in the subarachnoid space are surrounded by CSF and become penetrating arteries upon entering the brain parenchyma. Penetrating arteries are surrounded by CSF in perivascular (Virchow-Robin) spaces. Arterial wall pulsations drive CSF into the brain along perivascular spaces. As penetrating arteries become arterioles and capillaries, the CSF-filled perivascular spaces narrow and finally disappear, but the extracellular matrix of the basal lamina provides a perivascular conduit for continued CSF flow around arterioles and capillaries. Aquaporin-4 (AQP4) water channels on astrocyte end feet surrounding the perivascular space facilitate entry of CSF into the brain parenchyma. CSF mixes with interstitial fluid in the brain and moves by bulk flow through the brain parenchyma to perivenous spaces. Fluid drains from perivenous spaces out of the brain by meningeal and cervical lymphatics, along cranial and spinal nerves, and possibly through arachnoid granulations.

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KEY POINTS

- **Hyperventilation should primarily be used as a transient intervention to bridge a patient to a more definitive intracranial pressure therapy because it can induce cerebral ischemia.**
- **The glymphatic system consists of perivascular spaces through which CSF flows into the brain, driven by the pulsations of the arterial wall and facilitated by aquaporin-4 channels on astrocyte end feet.**

lymphatics.[62] Although many features of glymphatic function remain under debate or entirely unknown, the observation of this system by many independent groups has resulted in its existence being widely accepted. The glymphatic system likely went unrecognized until recent times because of the absence of high-resolution in vivo imaging and because the perivascular spaces collapse after death and may be obliterated with postmortem tissue preparation.[62]

The precise processes by which glymphatic function might contribute to cerebral edema formation are yet to be fully delineated, but several lines of evidence suggest a critical role. Recently, CSF was demonstrated to be the source of fluid influx responsible for early brain swelling after ischemic stroke.[5] In a mouse model of ischemic stroke, accelerated CSF influx into the brain parenchyma along perivascular spaces was observed within minutes of stroke. This CSF influx followed the wave of spreading depolarization that occurred with the loss of ionic gradients during cellular death and appeared to be the result of parenchymal and pial arteriole vasoconstriction precipitated by the spreading depolarization.[5] Interestingly, the magnitude of CSF influx was reduced in AQP4-deficient mice. The authors acknowledged that this process would not completely explain cerebral edema formation after ischemic stroke but proposed that it could also contribute to cerebral edema formation in other diseases in which spreading depolarizations have been observed, such as subarachnoid hemorrhage, intracerebral hemorrhage, and TBI.[5] Glymphatic dysfunction in clearing toxic substances, such as reactive oxygen and nitrogen species and inflammatory cytokines, could also contribute to cerebral edema. For example, reactive oxygen and nitrogen species might lead to cerebral edema through activation of ionic transporters (ie, the Na-K-Cl cotransporter 1), activation of intracellular protein kinase signaling cascades, blood-brain barrier disruption by activation of matrix metalloproteinases, or failure of oxidative phosphorylation through mitochondrial membrane pore formation and depolarization.[1,63] Furthermore, accumulation of brain cytokines, including tumor necrosis factor-α and transforming growth factor beta, from local and systemic inflammation can exacerbate vasogenic edema through disruption of blood-brain barrier tight junction proteins and upregulation of metalloproteinases.[1]

Given its prominent role in facilitating fluid movement through the brain, AQP4 might be an intuitive target for developing new cerebral edema therapies. For example, AQP4 membrane expression is increased after hypoxic central nervous system injury, and inhibiting this increased expression with trifluoperazine reduced edema and improved functional outcome in a rat model.[64] However, although AQP4-deficient mice demonstrate reduced cerebral edema in models of cytotoxic edema (cerebral ischemia and acute liver failure), cerebral edema is worse in AQP4-deficient models of vasogenic edema (tumors, subarachnoid hemorrhage, and abscesses).[1,6] Since most acute brain injury involves a mixture of cerebral edema types that evolve at different points in the disease, the pathophysiology around AQP4 and cerebral edema evolution will likely need greater clarification before AQP4 is an actionable therapeutic target.

Modifying the function of ion cotransporters and ion channels could also represent a therapeutic approach for cerebral edema. Na-K-Cl cotransporter 1 plays a prominent role in ionic hemostasis and water transport, and its activity is upregulated shortly after TBI and during acute liver failure. In addition to contributing to cytotoxic edema, Na-K-Cl cotransporter 1 also appears to be involved in the regulation of AQP4 and metalloproteinases with implications for blood-brain barrier integrity.[1,6] Although bumetanide has shown promise in animal models as a Na-K-Cl cotransporter 1 inhibitor, clinical data do not yet support therapies directed at this cotransporter for cerebral edema management. In contrast, clinical data are available to support the sulfonylurea receptor-1–transient receptor potential melastatin 4 (SUR1-TRPM4) ion channel as a

therapeutic target. The SUR1-TRPM4 channel regulates inorganic cation transport in the brain. SUR1-TRPM4 is unique in that it is not normally expressed in the brain but is upregulated following brain injury with intracellular ATP depletion, promoting channel opening, cellular depolarization, and cytotoxic edema with the potential for vasogenic edema if endothelial cells are involved.[6] Therefore, therapies directed at SUR1-TRPM4 would have the theoretic benefit of being selective for injured cells. Glyburide (glibenclamide) binds the SUR1 portion of SUR1-TRPM4 and blocks the channel's function. Glyburide is also an indirect inhibitor of matrix metalloproteinase-9, which could have implications for blood-brain barrier integrity and vasogenic edema. The phase 2 GAMES-RP (Glyburide Advantage in Malignant Edema and Stroke – Remedy Pharmaceuticals) trial demonstrated reduced brain compression and matrix metalloproteinase-9 levels in patients with severe anterior circulation stroke at risk for malignant cerebral edema who were treated with IV glyburide; however, the trial was underpowered to demonstrate a mortality or functional outcome benefit.[65] A randomized clinical trial of 66 patients with severe TBI demonstrated a reduced rate of contusion expansion but no difference in clinical outcome in patients who received oral glyburide.[66] Glyburide is currently being investigated in a clinical trial of TBI[67] and a phase 3 trial of large hemispheric ischemic stroke.[68]

The few specific cellular targets discussed here by no means represent the extent of agents and mechanisms that are being investigated for potential therapeutic effect on cerebral edema[6]; however, even this partial list suggests that our current therapeutic approach to cerebral edema is far from optimized. The list of potential therapies will likely continue to grow as our understanding of the mechanisms underlying cerebral edema deepens.

KEY POINT

- **CSF influx along perivascular spaces may provide the source of early cerebral edema after acute ischemic stroke.**

CONCLUSION

Cerebral edema, brain compression, and elevated ICP represent major causes of secondary brain injury that contribute to morbidity and mortality in neurocritical care. The current management of these conditions is based primarily on core physiologic principles and a limited number of interventions that have nonspecific effects on cerebral edema and brain compression. Over time, our knowledge of how to implement these interventions has been refined, but unexpected results from clinical trials suggest that our knowledge of acute brain injury pathophysiology remains incomplete. As our understanding of the glymphatic system and the cellular mechanisms of fluid regulation in the brain improves, we may learn how to better implement existing therapies and may identify new therapies that address specific cerebral edema mechanisms. We may also find that our classic conceptual models of cerebral edema and ICP are overly simplistic approximations in need of revision.

REFERENCES

1 Liotta EM, Kimberly WT. Cerebral edema and liver disease: classic perspectives and contemporary hypotheses on mechanism. Neurosci Lett 2020; 721:134818. doi:10.1016/j.neulet.2020.134818

2 Stokum JA, Kurland DB, Gerzanich V, Simard JM. Mechanisms of astrocyte-mediated cerebral edema. Neurochem Res 2015;40(2):317-328. doi:10.1007/s11064-014-1374-3

3 Treggiari MM, Schutz N, Yanez ND, Romand JA. Role of intracranial pressure values and patterns in predicting outcome in traumatic brain injury: a systematic review. Neurocrit Care 2007;6(2): 104-112. doi:10.1007/s12028-007-0012-1

4 Becker K. Hypertensive encephalopathy, eclampsia, and reversible posterior leukoencephalopathy. Continuum (Minneap Minn) 2006;12(1, Critical Care Neurology):30-45. doi:10.1212/01.CON.0000290436.03194.34

5 Mestre H, Du T, Sweeney AM, et al. Cerebrospinal fluid influx drives acute ischemic tissue swelling. Science 2020;367(6483):eaax7171. doi:10.1126/science.aax7171

6 Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. Neuropharmacology 2019;145(pt B):230-246. doi:10.1016/j.neuropharm.2018.08.004

7 Palma L, Bruni G, Fiaschi AI, Mariottini A. Passage of mannitol into the brain around gliomas: a potential cause of rebound phenomenon. A study on 21 patients. J Neurosurg Sci 2006;50(3): 63-66.

8 Liotta EM, Romanova AL, Lizza BD, et al. Osmotic shifts, cerebral edema, and neurologic deterioration in severe hepatic encephalopathy. Crit Care Med 2018;46(2):280-289. doi:10.1097/CCM.0000000000002831

9 Osgood M, Compton R, Carandang R, et al. Rapid unexpected brain herniation in association with renal replacement therapy in acute brain injury: caution in the neurocritical care unit. Neurocrit Care 2015;22(2):176-183. doi:10.1007/s12028-014-0064-y

10 Broocks G, Flottmann F, Scheibel A, et al. Quantitative lesion water uptake in acute stroke computed tomography is a predictor of malignant infarction. Stroke 2018;49(8):1906-1912. doi:10.1161/STROKEAHA.118.020507

11 Urday S, Kimberly WT, Beslow LA, et al. Targeting secondary injury in intracerebral haemorrhage–perihaematomal oedema. Nat Rev Neurol 2015; 11(12):111-122. doi:10.1038/nrneurol.2014.264

12 Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. Lancet Neurol 2006;5:53-63.

13 Feickert HJ, Drommer S, Heyer R. Severe head injury in children: impact of risk factors on outcome. J Trauma 1999;47(1):33-38. doi:10.1097/00005373-199907000-00008

14 Smith M. Monitoring intracranial pressure in traumatic brain injury. Anesth Analg 2008;106(1): 240-248. doi:10.1213/01.ane.0000297296.52006.8e

15 Rosner MJ, Becker DP. Origin and evolution of plateau waves. Experimental observations and a theoretical model. J Neurosurg 1984;60(2): 312-324. doi:10.3171/jns.1984.60.2.0312

16 Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery 2017;80(1): 6-15. doi:10.1227/NEU.0000000000001432

17 Lazaridis C, Desai M, Damoulakis G, Zeiler FA. Intracranial pressure threshold heuristics in traumatic brain injury: one, none, many! Neurocrit Care 2020;32(3):672-676. doi:10.1007/s12028-020-00940-4

18 Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46(7):2032-2060. doi:10.1161/STR.0000000000000069

19 Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med 1999;27(10): 2086-2095. doi:10.1097/00003246-199910000-00002

20 Allen BB, Chiu YL, Gerber LM, et al. Age-specific cerebral perfusion pressure thresholds and survival in children and adolescents with severe traumatic brain injury*. Pediatr Crit Care Med 2014;15(1):62-70. doi:10.1097/PCC.0b013e3182a556ea

21 Wang A, Ortega-Gutierrez S, Petersen NH. Autoregulation in the Neuro ICU. Curr Treat Options Neurol 2018;20(6):20. doi:10.1007/s11940-018-0501-x

22 Agrawal D, Raghavendran K, Zhao L, Rajajee V. A prospective study of optic nerve ultrasound for the detection of elevated intracranial pressure in severe traumatic brain injury. Crit Care Med 2020;48(12):e1278-e1285. doi:10.1097/CCM.0000000000004689

23 de Riva N, Budohoski KP, Smielewski P, et al. Transcranial Doppler pulsatility index: what it is and what it isn't. Neurocrit Care 2012;17(1):58-66. doi:10.1007/s12028-012-9672-6

24 Vaquero J, Fontana RJ, Larson AM, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl 2005;11(12): 1581-1589. doi:10.1002/lt.20625

25 Karvellas CJ, Fix OK, Battenhouse H, et al. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med 2014; 42(5):1157-1167. doi:10.1097/CCM.0000000000000144

26 Narayan RK, Kishore PR, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. J Neurosurg 1982;56(5):650-659. doi:10.3171/jns.1982.56.5.0650

27 Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 2012;367(26):2471-2481. doi:10.1056/NEJMoa1207363

28 Maas MB, Jahromi BS, Batra A, et al. Magnesium and risk of bleeding complications from ventriculostomy insertion. Stroke 2020;51:2795-2800. doi:10.1161/STROKEAHA.120.030128

29 Liotta EM, Lizza BD, Romanova AL, et al. 23.4% saline decreases brain tissue volume in severe hepatic encephalopathy as assessed by a quantitative computed tomography marker. Crit Care Med 2016;44(1):171-179. doi:10.1097/CCM.0000000000001276

30 Mindermann T. Pressure gradients within the central nervous system. J Clin Neurosci 1999;6(6):464-466. doi:10.1016/s0967-5868(99)90001-2

31 Posner JB, Saper CB, Schiff N, Plum F. Plum and Posner's diagnosis of stupor and coma. 4th ed. New York: Oxford University Press, 2007.

32 Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocrit Care 2014;21(suppl 2):S1-S26. doi:10.1007/s12028-014-0041-5

33 Bain oxygen optimization in severe TBI, phase 3 (BOOST3). ClinicalTrials.gov identifier: NCT03754114. Updated March 24, 2021. Accessed August 9, 2021. clinicaltrials.gov/ct2/show/NCT03754114?term=NCT03754114&draw=2&rank=1

34 Okonkwo DO, Shutter LA, Moore C, et al. Brain oxygen optimization in severe traumatic brain injury phase-II: a phase II randomized trial. Crit Care Med 2017;45(11):1907-1914. doi:10.1097/CCM.0000000000002619

35 Boussen S, Lagier D, Velly LJ, Bruder NJ. Brain oxygen optimization in severe traumatic brain injury and outcome. Crit Care Med 2018;46(4):e349-e350. doi:10.1097/CCM.0000000000002957

36 Venkatasubramanian C, Lopez GA, O'Phelan KH, et al. Emergency neurological life support: fourth edition, updates in the approach to early management of a neurological emergency. Neurocrit Care 2020;32(2):636-640. doi:10.1007/s12028-019-00810-8

37 Curtis CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166(10):1338-1344. doi:10.1164/rccm.2107138

38 Clayton TJ, Nelson RJ, Manara AR. Reduction in mortality from severe head injury following introduction of a protocol for intensive care management. Br J Anaesth 2004;93(6):761-767. doi:10.1093/bja/aeh249

39 Miller CM, Pineda J, Corry M, et al. Emergency Neurologic Life Support (ENLS): evolution of management in the first hour of a neurological emergency. Neurocrit Care 2015;23 suppl 2:S1-S4. doi:10.1007/s12028-015-0170-5

40 Dietrich J, Rao K, Pastorino S, Kesari S. Corticosteroids in brain cancer patients: benefits and pitfalls. Expert Rev Clin Pharmacol 2011;4(2):233-242. doi:10.1586/ecp.11.1

41 Ryken TC, Kuo JS, Prabhu RS, et al. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of steroids in the treatment of adults with metastatic brain tumors. Neurosurgery 2019;84(3):E189-E191. doi:10.1093/neuros/nyy546

42 Binnahil M, Au K, Lu JQ, et al. The influence of corticosteroids on diagnostic accuracy of biopsy for primary central nervous system lymphoma. Can J Neurol Sci 2016;43(5):721-725. doi:10.1017/cjn.2016.255

43 Patel K, Clifford DB. Bacterial brain abscess. Neurohospitalist 2014;4(4):196-204. doi:10.1177/1941874414540684

44 Cook AM, Morgan Jones G, Hawryluk GWJ, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. Neurocrit Care 2020;32(3):647-666. doi:10.1007/s12028-020-00959-7

45 Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 2004;364(9442):1321-1328. doi:10.1016/S0140-6736(04)17188-2

46 Sandercock PA, Soane T. Corticosteroids for acute ischaemic stroke. Cochrane Database Syst Rev 2011;2011(9):CD000064. doi:10.1002/14651858.CD000064.pub2

47 Wang J, Fang Y, Ramesh S, et al. Intraosseous administration of 23.4% NaCl for treatment of intracranial hypertension. Neurocrit Care 2019;30(2):364-371. doi:10.1007/s12028-018-0637-2

48 Hirsch KG, Spock T, Koenig MA, Geocadin RG. Treatment of elevated intracranial pressure with hyperosmolar therapy in patients with renal failure. Neurocrit Care 2012;17(3):388-394. doi:10.1007/s12028-012-9676-2

49 Koenig MA, Bryan M, Lewin JL 3rd, et al. Reversal of transtentorial herniation with hypertonic saline. Neurology 2008;70(13):1023-1029. doi:10.1212/01.wnl.0000304042.05557.60

50 McDowell ME, Wolf AV, Steer A. Osmotic volumes of distribution; idiogenic changes in osmotic pressure associated with administration of hypertonic solutions. Am J Physiol 1955;180(3):545-558. doi:10.1152/ajplegacy.1955.180.3.545

51 Liotta EM, Karvellas CJ, Kim M, et al. Serum osmolality, cerebrospinal fluid specific gravity and overt hepatic encephalopathy severity in patients with liver failure. Liver Int 2020;40(8):1977-1986. doi:10.1111/liv

52 Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49(3):e46-e110. doi:10.1161/STR.0000000000000158

53 Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 2011;364(16):1493-1502. doi:10.1056/NEJMoa1102077

54 Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med 2016;375(12):1119-1130. doi:10.1056/NEJMoa1605215

55 Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. Lancet 2019;393(10175):1021-1032. doi:10.1016/S0140-6736(19)30195-3

56 Cooper DJ, Nichol AD, Bailey M, et al. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury: the POLAR Randomized Clinical Trial. JAMA 2018;320(21):2211-2220. doi:10.1001/jama.2018.17075

57 Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. Neurochem Res 2015;40(12):2583-2599. doi:10.1007/s11064-015-1581-6

58 Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 2012;4(147):147ra11. doi:10.1126/scitranslmed.3003748

59 Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. Nature 2015;523(7560):337-341. doi:10.1038/nature14432

60 Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 2015;212(7):991-999. doi:10.1084/jem.20142290

61 Mestre H, Tithof J, Du T, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nat Commun 2018;9(1):4878. doi:10.1038/s41467-018-07318-3

62 Mestre H, Mori Y, Nedergaard M. The brain's glymphatic system: current controversies. Trends Neurosci 2020;43(7):458-466. doi:10.1016/j.tins.2020.04.003

63 Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurol 2018;17(11):1016-1024. doi:10.1016/S1474-4422(18)30318-1

64 Kitchen P, Salman MM, Halsey AM, et al. Targeting aquaporin-4 subcellular localization to treat central nervous system edema. Cell 2020;181(4):784-799.e19. doi:10.1016/j.cell.2020.03.037

65 Sheth KN, Elm JJ, Molyneaux BJ, et al. Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2016;15(11):1160-1169. doi:10.1016/S1474-4422(16)30196-X

66 Khalili H, Derakhshan N, Niakan A, et al. Effects of oral glibenclamide on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injuries: a randomized double-blind placebo-controlled clinical trial. World Neurosurg 2017;101:130-136. doi:10.1016/j.wneu.2017.01.103

67 Glyburide (RP-1127) for traumatic brain injury (TBI). ClinicalTrials.gov identifier: NCT01454154. Updated June 21, 2021. Accessed August 9, 2021. clinicaltrials.gov/ct2/show/NCT01454154?term=NCT01454154&draw=2&rank=1

68 Phase 3 study to evaluate the efficacy and safety of intravenous BIIB093 (glibenclamide) for severe cerebral edema following large hemispheric infarction (CHARM). ClinicalTrials.gov identifier: NCT02864953. Updated July 20, 2021. Accessed August 9, 2021. clinicaltrials.gov/ct2/show/NCT02864953?term=NCT02864953&draw=2&rank=1